Linking 'omic and Genetic Data to Physiologically-Based Pharmacokinetic and Pharmacodynamic Modeling to Enhance Ecological and Human Health Risk Assessment

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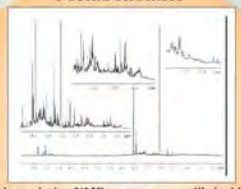
Objective:

Enhance ecological and human health risk assessment through a collaborative U.S. EPA/ORD project that will be one of the first attempts to integrate 'omics data and Physiologically-Based Pharmacokinetic and Pharmacodynamic (PBPK/PD) modeling.

Approach:

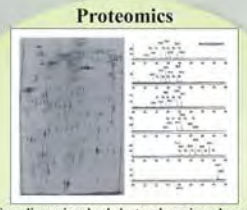
Use molecular, tissue-level, and whole organism endpoints to examine dose phenomena in zebrafish (*Danio rerio*) following exposure to a prototypical chemical, such as an OP or carbamate pesticide. Develop a predictive model by comparing these results to a preliminary model and improving the model by incorporating new data where appropriate.

Metabonomics



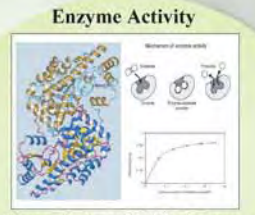
High-resolution NMR spectroscopy will elucidate changes in metabolite patterns that will help identify toxicity patterns associated with chemical exposure.

Proteomics



Two-dimensional gel electrophoresis and mass spectrometry will identify differentially expressed proteins, which are directly responsible for mediating the cellular response and can be used to identify associated transcriptional changes.

Enzyme Activity



The concentration and activity of enzymes involved with the metabolism of or altered by the exposure chemical will be measured, as will tissue and whole-organism chemical concentrations.

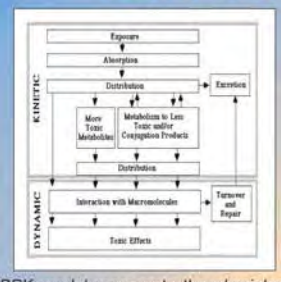
Genomics

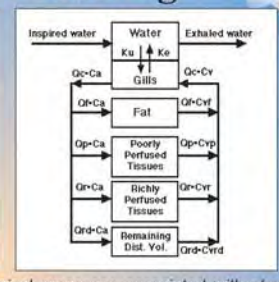
Microarrays will identify differentially expressed genes and gene pathways, which will function as molecular biomarkers of exposure (QPCR) and help identify the mode of action and subsequent effects associated with chemical exposure.

Histopathology

H&E staining, immunohisto/cytochemistry, and *in situ* hybridization of targeted tissues will identify altered tissue development or function, helping to link effects data with molecular indices of exposure.

PBPK/PD Modeling





A PBPK model represents the physiological processes associated with chemical adsorption, distribution, metabolism, and excretion (ADME). A PD model represents the toxicity phase, when a response is elicited at the target site(s) driving physiological and behavioral responses. The 'omic and genetic data will be incorporated into the models to enhance risk assessment.

Genetics

DNA sequence polymorphisms and other genetic technologies will provide an opportunity to study the extent to which variations in pharmacologic parameters can be explained by genetics.

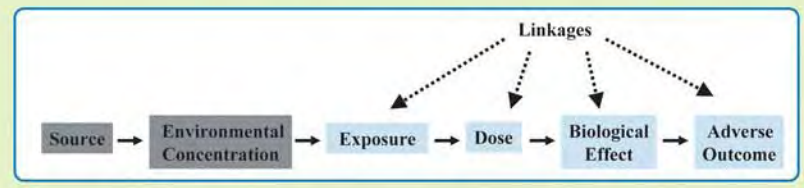
Whole Organism

Reproductive (fecundity/fertility) developmental (hatching/feeding), behavioral (various swimming aspects), and mortality (LC_{50} values) tests will guide exposure dose and duration regimens and phenotypically anchor effect and exposure.

Ecological and Human Health Risk Assesment

Outcomes:

1) Identify and compare novel dose- and time-dependent indicators across multiple biological levels.
2) Evaluate the relevance and linkage of biological data generated from multiple experimental platforms.
3) Form linkages across the source-to-outcome continuum (shown at right):
4) Incorporate 'omic and genetic data into PBPK/PD models.
5) Enhance ecological and human health risk assessments by reducing the uncertainty in the exposure component.
6) Evaluate basic and cost efficient ecological (invertebrate and fish) models as potential substitutes for more complex and expensive human health (mice and rats) models.



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